REMARKS

Claims 1-15 and 24-37 and 41 are pending. Claims 16-18, 21-23, and 38-40 were previously withdrawn from consideration as being drawn to non-elected species. However, Applicants reserve the right to have the withdrawn claims examined upon indication of an allowable generic claim.

I. Withdrawal of Rejections

Applicants thank the Examiner for indication of the withdrawal of the enablement rejections of the claims set forth in the previous Office Action.

II. Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-15, 24-37 and 41 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way so as to enable those skilled in the art to make and/or use the invention. This rejection is respectfully traversed for at least the reasons which follow.

More specifically, the Examiner asserts that the specification, "while being enabling for claims limited in scope to a method for lowering triglyceride levels in a subject having diabetes, does not reasonably provide enablement for claims to a method for lowering triglyceride levels in any subject in need thereof." Applicants respectfully traverse this rejection.

Applicants have provided considerable direction and guidance, and have presented working examples such that it is well within the level of ordinary skill in the art to practice the claimed invention without undue experimentation. For example, the specification discusses the measurement of fasting triglyceride levels, as well as the observed association of elevated postprandial triglyceride levels with cardiovascular disease and the effects of exendins on the postprandial triglyceride levels of diabetics. *See Specification*, page 4, third full paragraph, including the references cited therein, and Example 186. The specification also discusses the association of elevated triglyceride levels with various disease states, including diabetes, pancreatitis, and cardiovascular disease. *See Specification*, pages 2-4. Moreover, the invention is described as including the modulation of fasting triglycerides, the modulation of postprandial triglyceride levels,

as well as the modulation of both fasting and postprandial triglyceride levels. *See Specification*, paragraph bridging pages 12 and 13. Further, elevated triglyceride levels are discussed as "any degree of triglyceride levels that is determined to be undesirable or is targeted for modulation." *Specification*, page 12, first full paragraph. Taken in combination, such disclosure provides adequate direction to those skilled in the art of how to make and use the claimed invention.

The Examiner alleges, however, that "such treatment would not be suitable for non-diabetic subjects merely having elevated postprandial triglyceride levels because an exendin, would inherently lower the blood glucose levels, which would be dangerous for the treated subject whose blood glucose levels are not elevated." *Id.* at page 3. The Examiner goes on to assert that, hypoglycemia was reported as one of "the most frequent adverse events," *Id.* at page 3. In this regard, Applicants note that the Examiner is referring to an example of the present specification involving clinical testing where "[r]eported adverse events, EKG, physical exam, and safety lab monitoring revealed no safety issues. Nausea, vomiting and hypoglycemia were the most frequent adverse events, however all were reported as mild in intensity." *Specification* at page 149 (emphasis added). The Examiner has not provided any evidence that treatment of subjects using the claimed methods would result in allegedly dangerous side effects. Applicants wish to respectfully point out that it is well established in the art that the ability of exendins to stimulate insulin secretion is glucose dependent. That is, exendins stimulate insulin secretion during euglycemia and hyperglycemia, but not hypoglycemia. Nielsen et al., *Regulatory Peptides*, 117:77-88, 2004. Thus, the allegation that the claimed method is dangerous is unsubstantiated by any objective evidence of record and contrary to the teachings in the art. Absent such evidence, the Applicants' disclosure must be taken by the Patent Office as enabling. *In re Marzocchi*, 439 F.2d 220 (CCPA 1971)

In accordance with Section 2107.03 of the Manual of Patent Examining Procedure, the Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the

advertisement, use, sale or distribution of drugs. The Food and Drug Administration is the government agency responsible for evaluating the safety and efficacy of a drug product, while the Office is responsible for applying the patent laws. Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness. *See In re Sichert*, 566 F.2d 1154, 196 U.S.P.Q. 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 U.S.P.Q. 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 U.S.P.Q. 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 U.S.P.Q. 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 U.S.P.Q. 215 (CCPA 1961); *Ex parte Jovanovics*, 211 U.S.P.Q. 907 (Bd. Pat. App. & Inter. 1981).

Addressing the Patent Office's contention that due to the possibility of hypoglycemia the practice of the claimed method would require undue experimentation, Applicant again respectfully points out that this contention is unsupported by any evidence of record. Even assuming, *arguendo*, that the Examiner's generalization regarding the unpredictable state of the art is accepted, the conclusion that undue experimentation would be required is inconsistent with the current state of the law. Specifically, the law provides that experimentation is not necessarily undue simply because it is complex, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174, (Int'l Trade Comm'n 1983) *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). In this regard, based on the teachings of the present specification and the knowledge of those skilled in the art, a trained clinician is more than capable of monitoring subjects treated with the methods of the present invention for side effects.

As such, it is submitted that Applicants have provided considerable direction and guidance, and have presented working examples such that it is well within the level of ordinary skill in the art to practice the invention without undue experimentation. The Examiner has not provided sufficient evidence to cast doubt on the guidance provided in the specification. Rather, the Examiner has provided generalizations regarding a lack of

predictability in the art and the need for some experimentation to "determine if the claimed method could be practiced on non-diabetics."

An analysis of the *In re Wands* criteria also supports Applicants' position that no undue experimentation would be required to make and use the claimed invention. *See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1998). The first *Wands* criterion is the quantity of experimentation necessary. The "make-and-test" quantum of experimentation is reduced by the extensive knowledge to which a person of ordinary skill in the art has access. Performing routine and well-known steps, such as clinical assays to determine plasma triglyceride levels in a postprandial state and monitoring subjects, cannot create undue experimentation, even if it is laborious. *See In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 218-219 (CCPA 1976).

The second and third *Wands* criteria relate to the amount of direction or guidance given, and the presence or absence of working examples. As discussed above, the present specification provides ample guidance and direction in the form of, *e.g.*, a discussion of the association between elevated postprandial triglyceride levels and various disease states and disorders, the modulation of postprandial triglyceride levels, and working examples showing the same.

The fourth, fifth, and sixth *Wands* criteria focus on the nature of the invention, the state of the art, and the relative skill in the art. The present invention relates to methods for lowering postprandial triglyceride levels in a subject with elevated postprandial triglyceride levels by administering exendin compounds. Considerable knowledge and resources guide practitioners in this art as to the conditions and approaches that can be utilized to perform such therapeutic methods, as evidenced by the references cited in the specification and the additional references made of record. Many resources are readily available to the skilled art worker. Moreover, as discussed above, the present specification itself adds to the relative skill in the art by providing detailed guidance regarding the application of such techniques to the art of the present invention. Such resources, combined with the specification and the general knowledge of those skilled in the art provide ample guidance to enable one of ordinary skill in the art to make and use the claimed invention.

The seventh criterion considers the predictability of the art. The Examiner alleges that "it is not predictable whether any or all subjects having elevated postprandial triglyceride levels are suitable for the treatment with an exendin, which has the primary role in lowering blood glucose levels." Office Action at page 3. . The skilled artisan, however, can readily monitor blood glucose levels using well-known procedures. Recognition of such an effect and the appropriate action are well within the skill of the ordinary clinician. Further, it is submitted that the specification discloses sufficient guidance to render the results predictable within the context of the invention. In fact, by providing guidance by discussion of the modulation of postprandial triglyceride levels, and exemplification of the same, Applicants have demonstrated that the present invention yields a predicted result.

The eighth criterion focuses on the breadth of the claims. Enablement is satisfied when the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck,* 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). In the present case, one of skill in the art is specifically guided by the disclosure of a method of lowering postprandial triglyceride levels in a subject in need thereof, including identifying such a subject, *i.e.*, those with elevated postprandial triglyceride levels. As such, based on the teachings of the specification, one of skill in the art would be able to ascertain which subjects exhibit elevated postprandial triglyceride levels as a target for therapeutic lowering, thereby possessing the disclosed utility and falling within the scope of the claims. It is thus submitted that the specification provides enablement commensurate in scope with the claims.

Accordingly, for at least these reasons, it is submitted that the claims are sufficiently enabled under 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

III. Rejection under 35 U.S.C. § 103(a)

Claims 1-14, 24-36 and 41 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Karpe, *et al.*, "and in view of Beeley et al. WO 98/30231)... and Beers et al. (the Merck Manual, 1999, 17th edition, pages 200 and 2550)." Office Action

at page 4. Applicants respectfully disagree and traverse for at least the reasons that follow.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, and not be based on applicant's disclosure. *See* M.P.E.P. §§2143.01 and 2143.03.

The present claims relate to the lowering of triglyceride levels. The claimed methods include identifying a patient with elevated triglyceride levels (or elevated postprandial triglyceride levels), followed by the administration of a therapeutically effective amount of an exendin or an exendin agonist.

As previously discussed, Beeley does not discuss the use of exendins in the reduction of triglycerides specifically (triglycerides are a subset of total plasma lipids, which include, *e.g.*, LDL, HDL, VLDL, and cholesterol). Moreover, the discussions of the lowering of plasma lipids in Beeley are in the context of a reduction in food intake. As such, whatever else Beeley does disclose, the reference does not teach or suggest the identification of a subject having elevated postprandial triglyceride levels and the ability of exendins to specifically lower triglycerides in spite of constant food intake.

The Examiner alleges that "it is well established in the art, and evidenced by Beers that the triglycerides are *major* plasma lipids," and therefore "Beeley's method for lowering plasma lipids would inherently lower the triglyceride levels." Office Action at page 4. "Obviousness cannot be predicated on what is unknown." *In re Newell*, 891 F.2d 399, 901 (Fed. Cir. 1989), citing *In re Spormann*, 363 F.2d 444, 448, 53 C.C.P.A. 1375, 1380, 150 U.S.P.Q. 449, 452 (1966). In establishing a *prima facie* case, the Examiner, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention, and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success

must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed inventions, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002)(citations and quotes omitted). Additionally, it is now well-established that "[b]road conclusory statements regarding the teaching of multiple references standing alone are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also, *In re Kotzab*, 217 F.3d at 1370. Beeley does not teach or suggest the identification of a subject with elevated postprandial triglyceride levels, followed by the administration of a therapeutically effective amount of an exendin or exendin agonist. In addition, the Examiner has not shown by objective evidence that one skilled in the art would reasonably expect the methods of Beeley, *et al.* to reduce the postprandial triglyceride levels absent the reduction of food intake. Applicants respectfully submit, therefore, that the Examiner has not met his burden of establishing a *prima facie* obviousness case.

Moreover, and as the Examiner acknowledges, "Karpe does not teach a method for lowering triglyceride levels with an exendin." Office Action at page 4. Accordingly, Karpe, *et al.* does not remedy the deficiencies of Beeley, *et al.* and Beers, *et al.* As such, the cited references taken in combination do not teach or suggest the claimed methods. For at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a)of claims 1-14, 24-36 and 41.

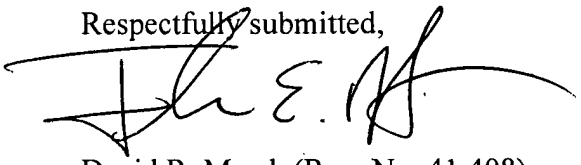
Claims 15 and 37 also stand rejected under 35 U.S.C. §103(a) as alleged being unpatentable over Karpe, *et al.*, Beeley, *et al.*, and Beers, *et al.* in view of Wagle *et al.* US 6,326,396 B1 (hereinafter, "Wagle"). This rejection is respectfully traversed. Whatever else Wagle *et al.* does disclose, it too does not recognize the ability of exendins to lower postprandial plasma triglycerides as an independent mode of action. As such, Wagle *et al.* does not remedy the deficiencies of Karpe, Beeley, and Beers in this regard.

In sum, it is submitted that the cited references do not disclose or suggest the ability of exendins to specifically lower triglyceride levels. As such, the cited references do not render the present claims obvious. For at least the foregoing reasons, it is respectfully submitted that all of the pending claims are non-obvious over the prior art of record, since at a minimum they do not include or suggest the aforementioned limitations. As such, withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-5085 should any additional information be necessary for allowance.

Respectfully submitted,



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